M. Hawkins 14.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

18 JUN 1991

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: Health Effects Division (HED) Peer Review Committee
Draft Document on **Parathion (3rd)**

FROM: Esther Rinde, Ph.D. E.R.
Manager, HED Carcinogenicity Peer Review
Science Analysis Coordination Branch
Health Effects Division (H7509C)

DC 057501

TO: Addressees

Attached for your review is the draft document of the Peer Review Committee on **Parathion (3rd)**. Please provide your comments on the draft document and return to me no later than **June 25, 1991.** If a reply is not received by that time, we will presume that you concur and have no comments.

Should you need a few extra days for a thorough review, please let us know that your comments are forthcoming.

ADDRESSEES

P. Fenner-Crisp
W. Burnam
R. Engler
R. Hill
K. Baetcke
R. Beliles
L. Brennecke
M. Copley
K. Dearfield
J. Du
B. Fisher
G. Ghali
H. Pettigrew
J. Parker
W. Sette
M. Van Gemert
Y. Woo
J. Quest
R. Zendzian

MEMORANDUM

SUBJECT: DRAFT Peer Review of Parathion (3rd)

FROM: Esther Rinde, Ph.D. ER 6/14/91
Science Analysis and
Coordination Branch
Health Effects Division (H7509c)

TO: Jan Auerbach, Chief
Special Review Branch
Special Review and Reregistration Division (H7508c)

The Health Effects Division Peer Review Committee met on June 12, 1991 to discuss and evaluate new data on Parathion with particular reference to its bearing on the classification of Parathion's carcinogenic potential. The Committee concluded that the new data does not affect the existing classification and Parathion remains classified as a **Group C (possible human carcinogen) without quantification,** which is to say: without the use of a low dose exrapolation model (Q1*) for quantitative risk assessment; instead a reference dose (RfD) approach will be used.

A. Individuals in Attendance:

1. Peer Review Committee: (Signatures indicate concurrence with the peer review unless otherwise stated.)

William L. Burnam _____
Reto Engler _____
Marcia Van Gemert _____
Karl Baetcke _____
Robert Beliles _____
Lucas Brennecke _____
Marion Copley _____
Kerry Dearfield _____
Hugh Pettigrew _____
Esther Rinde _____

2. Reviewers: (Non-committee members responsible for data presentation; signatures indicate technical accuracy of panel report.)

Robert Zendzian _____
Bernice Fisher _____

3. Peer Review Members in Absentia: (Committee members who were unable to attend the discussion; signatures indicate concurrence with the overall conclusions of the Committee.)

Penelope A. Fenner-Crisp _____
Julie Du _____
George Ghali _____
Richard Hill _____
Jean Parker _____
William Sette _____
Yin-Tak Woo _____
John Quest _____

B. Material Reviewed:

The material available for review consisted of a DER and summary memo prepared by Dr. Zendzian; Tables and statistical analysis were provided by the Registrant (HED statistician, Ms. Fisher determined that additional analysis was not warranted); Peer Review Documents for the 1st and 2nd meetings, dated Sept. 8, 1986 and July 31, 1989, respectively. The material reviewed is attached to the file copy of this report.

C. Background Information:

Parathion, a special review chemical, was classified as a Group C (possible human carcinogen) without quantitative risk assessment by the Peer Review Committee (PRC) at its meetings on July 1, 1986 and on March 7, 1989. A new mouse study, submitted by the Registrant, has been reviewed and the PRC was asked to consider whether the new data have any bearing on the classification of Parathion.

PRESENTATION OF NEW DATA

Reference: Carcinogenicity study of ethyl parathion administered by dosed feed to B6C3F1 mice, J.G. Page & J.E. Heath, Southern Research Institute, Project ID A21-CRM-1, 1/21/91, MRID 418173-01.

a. Experimental Design

Parathion was administered in the diet to groups of 50 male and 50 female B6C3F1 mice at 0 (control), 60, 100 and 140 ppm for 18 months.

b. Discussion of Tumor Data

The only increases in tumor occurrence that were statistically significant were observed at 60 ppm; these were lung alveolar/bronchiolar adenomas in males and systemic malignant lymphoma in females (Tables 1 and 2 - taken from the Registrant's submission). The incidence of adenomas in male mice at 60 ppm exceeded the upper range reported for historical controls at the testing facility; the incidence of malignant lymphoma in females was within the range of historical controls (Tables 3 and 4).

A misdosing incident, however, involving this dose (60 ppm) "was reported to the Agency when detected and a joint decision was made to continue the study" [R. Zendzian].

> Dr. Zendzian quotes the Registrant's report as follows: "Due to a technical error in diet preparation, mice in the 60 ppm dose group were fed a diet containing approximately 500 ppm ethyl parathion between Days 300 and 307 of this study. The mice in this dose group were switched to control diet (i.e., untreated) diet (sic) following detection of the misdosing incident for 17 days (Days 300 to 323) to allow these mice to regain lost weight and recover from the acute toxicity induced by exposure to an excessive dose of test article. The incident is highlighted here because it had an impact on study parameters (e.g., mortalities, body weights, food consumption) and study interpretation." (Six males and two females died within 14 days of the misdosing.)

c. Consideration of Adequacy of Dosing for Assessment of Carcinogenic Potential:

Both male and female mice were considered to have been adequately, but not excessively dosed (at 140 ppm), based on dose-related decreases (less than 5%) in body-weight gain and significant brain, plasma and RBC cholinesterase inhibition (without a compound induced increase in mortality).

The low dosed animals ("60" ppm) were of course overdosed.

Table 1

CARCINOGENICITY STUDY OF ETHYL PARATHION ADMINISTERED BY DOSED FEED TO B6C3F1 MICE
Study: A21-CRM-1
Analysis of Histopathology Findings - Males
Tumor Pathology

	Untreated	60 PPM	100 PPM	140 PPM
Lung - Alveolar/Bronchiolar Adenoma				
Overall Rates (a)	5/50 (10.0%)	13/50 (26.0%)	6/50 (12.0%)	4/50 (8.0%)
Terminal Rates (b)	5/49 (10.2%)	12/39 (30.8%)	6/47 (12.8%)	4/50 (8.0%)
Life Table Test (c)		p = 0.009*	p = 0.471	p = 0.513
Incidental Tumor Test (d)		p = 0.014*	p = 0.457	p = 0.500
Cochran-Armitage Trend Test (e)	p = 0.206			
Fisher Exact Test (e)		p = 0.033*	p = 0.500	p = 0.500
Lung - Alveolar/Bronchiolar Carcinoma				
Overall Rates (a)	0/50	1/50 (2.0%)	0/50	0/50
Terminal Rates (b)	0/49	1/39 (2.6%)	0/47	0/50
Life Table Test (c)		p = 0.454	p = 1.000	p = 1.000
Incidental Tumor Test (d)		p = 0.450	p = 1.000	p = 1.000
Cochran-Armitage Trend Test (e)	p = 0.500			
Fisher Exact Test (e)		p = 0.500	p = 1.000	p = 1.000
Lung - Alveolar/Bronchiolar Adenoma and Carcinoma Combined				
Overall Rates (a)	5/50 (10.0%)	14/50 (28.0%)	6/50 (12.0%)	4/50 (8.0%)
Terminal Rates (b)	5/49 (10.2%)	13/39 (33.3%)	6/47 (12.8%)	4/50 (8.0%)
Life Table Test (c)		p = 0.005*	p = 0.471	p = 0.513
Incidental Tumor Test (d)		p = 0.007*	p = 0.457	p = 0.500
Cochran-Armitage Trend Test (e)	p = 0.185			
Fisher Exact Test (e)		p = 0.020*	p = 0.500	p = 0.500

Table 2

CARCINOGENICITY STUDY OF ETHYL PARATHION ADMINISTERED BY DOSED FEED TO B6C3F1 MICE
Study: A21-CRM-1
Analysis of Histopathology Findings - Females
Tumor Pathology

	Untreated	60 PPM	100 PPM	140 PPM
Harderian Gland - Adenoma				
Overall Rates (a)	1/50 (2.0%)	1/50 (2.0%)	0/50	0/50
Terminal Rates (b)	1/44 (2.3%)	1/42 (2.4%)	0/48	0/44
Life Table Test (c)		p = 0.751	p = 0.517	p = 0.500
Incidental Tumor Test (d)		p = 0.756	p = 0.517	p = 0.500
Cochran-Armitage Trend Test (e)	p = 0.170			
Fisher Exact Test (e)		p = 0.753	p = 0.500	p = 0.500
Systemic - Lymphoma Malignant				
Overall Rates (a)	0/50	5/50 (10.0%)	3/50 (6.0%)	2/50 (4.0%)
Terminal Rates (b)	0/44	3/42 (7.1%)	2/48 (4.2%)	1/44 (2.3%)
Life Table Test (c)		p = 0.033*	p = 0.140	p = 0.242
Incidental Tumor Test (d)		p = 0.033*	p = 0.060	p = 0.240
Cochran-Armitage Trend Test (e)	p = 0.332			
Fisher Exact Test (e)		p = 0.028*	p = 0.121	p = 0.247
Systemic - Histiocytic Sarcoma				
Overall Rates (a)	0/50	1/50 (2.0%)	0/50	2/50 (4.0%)
Terminal Rates (b)	0/44	0/42	0/48	0/44
Life Table Test (c)		p = 0.504	p = 1.000	p = 0.249
Incidental Tumor Test (d)		p = 0.500	p = 1.000	p = 0.223
Cochran-Armitage Trend Test (e)	p = 0.149			
Fisher Exact Test (e)		p = 0.500	p = 1.000	p = 0.247

CONTRACT/LAB: SRI
SPECIES: MICE
STRAIN: MICE-B6C3F1
LENGTH OF STUDY: CHRONIC

ROUTE: ORAL
VEHICLE: FEED

DATE OF
INPUT FILE: 15-SEP-1990

INCIDENCE DATA FOR VEHICLE CONTROL GROUPS

	MALE			FEMALE		
*LIVER:						
HEPATOCELLULAR CARCINOMA, HEPATOCELLULAR ADENOMA, HEPATOBLASTOMA OR NEOPLASTIC NODULE	10/50 (20%)	13/49 (27%)	12/50 (24%)	2/50 (4%)	8/50 (16%)	3/50 (6%)
TOTAL % INCIDENCE	35/149 (23%)	S.D. = 3.51		13/150 (9%)	S.D. = 6.43	
*LIVER:						
HEPATOCHOLANGIOCARCINOMA	0/50 (0%)	0/49 (0%)	0/50 (0%)	0/50 (0%)	0/50 (0%)	0/50 (0%)
TOTAL % INCIDENCE	0/149 (0%)	S.D. = 0.00		0/150 (0%)	S.D. = 0.00	
*LIVER:						
ITO CELL TUMOR BENIGN	0/50 (0%)	0/49 (0%)	0/50 (0%)	0/50 (0%)	0/50 (0%)	0/50 (0%)
TOTAL % INCIDENCE	0/149 (0%)	S.D. = 0.00		0/150 (0%)	S.D. = 0.00	
*LIVER:						
LEUKEMIA ERYTHROCYTIC	0/50 (0%)	0/49 (0%)	0/50 (0%)	0/50 (0%)	0/50 (0%)	0/50 (0%)
TOTAL % INCIDENCE	0/149 (0%)	S.D. = 0.00		0/150 (0%)	S.D. = 0.00	
*LIVER:						
SARCOMA	0/50 (0%)	0/49 (0%)	0/50 (0%)	0/50 (0%)	0/50 (0%)	0/50 (0%)
TOTAL % INCIDENCE	0/149 (0%)	S.D. = 0.00		0/150 (0%)	S.D. = 0.00	
*LUNG:						
ALVEOLAR/BRONCHIOLAR ADENOMA	8/50 (10%)	6/50 (12%)	5/50 (10%)	2/50 (4%)	3/50 (6%)	1/50 (2%)
TOTAL % INCIDENCE	16/150 (11%)	S.D. = 1.15		6/150 (4%)	S.D. = 2.00	
*LUNG:						
ALVEOLAR/BRONCHIOLAR ADENOMA OR ADENOMA	8/50 (10%)	6/50 (12%)	5/50 (10%)	2/50 (4%)	3/50 (6%)	1/50 (2%)
TOTAL % INCIDENCE	16/150 (11%)	S.D. = 1.15		6/150 (4%)	S.D. = 2.00	
*LUNG:						
ALVEOLAR/BRONCHIOLAR CARCINOMA	1/50 (2%)	3/50 (6%)	6/50 (12%)	1/50 (2%)	1/50 (2%)	2/50 (4%)
TOTAL % INCIDENCE	10/150 (7%)	S.D. = 5.03		4/150 (3%)	S.D. = 1.15	
*LUNG:						
ALVEOLAR/BRONCHIOLAR CARCINOMA OR ALVEOLAR/BRONCHIOLAR ADENOMA	6/50 (12%)	9/50 (18%)	11/50 (22%)	3/50 (6%)	4/50 (8%)	3/50 (6%)
TOTAL % INCIDENCE	26/150 (17%)	S.D. = 5.03		10/150 (7%)	S.D. = 1.15	
*LUNG:						
CARCINOMA	0/50 (0%)	0/50 (0%)	0/50 (0%)	0/50 (0%)	0/50 (0%)	0/50 (0%)
TOTAL % INCIDENCE	0/150 (0%)	S.D. = 0.00		0/150 (0%)	S.D. = 0.00	
*LUNG:						
CARCINOMA, ALVEOLAR/BRONCHIOLAR CARCINOMA OR ADENOSQUAMOUS CARCINOMA	1/50 (2%)	3/50 (6%)	6/50 (12%)	1/50 (2%)	1/50 (2%)	2/50 (4%)
TOTAL % INCIDENCE	10/150 (7%)	S.D. = 5.03		4/150 (3%)	S.D. = 1.15	

*: DENOMINATOR IS NUMBER OF ANIMALS WITH TISSUES EXAMINED MICROSCOPICALLY
#: DENOMINATOR IS NUMBER OF ANIMALS NECROPSIED

CONTRACT/LAB: SRI
SPECIES: MICE
STRAIN: MICE-B6C3F1
LENGTH OF STUDY: CHRONIC

ROUTE: ORAL
VEHICLE: FEED

DATE OF
INPUT FILE: 15-SEP-1990

INCIDENCE DATA FOR VEHICLE CONTROL GROUPS

	MALE			FEMALE		
ALL ORGANS BENIGN TUMORS TOTAL % INCIDENCE	12/50 (24%) 48/150 (32%)	18/50 (36%) S.D. = 6.93	18/50 (36%)	15/50 (30%) 39/150 (26%)	13/50 (26%) S.D. = 4.00	11/50 (22%)
ALL ORGANS MALIGNANT TUMORS TOTAL % INCIDENCE	28/50 (56%) 84/150 (56%)	30/50 (60%) S.D. = 4.00	26/50 (52%)	21/50 (42%) 60/150 (40%)	21/50 (42%) S.D. = 3.46	18/50 (36%)
ALL ORGANS MALIGNANT AND BENIGN TUMORS TOTAL % INCIDENCE	31/50 (62%) 105/150 (70%)	39/50 (78%) S.D. = 8.00	35/50 (70%)	30/50 (60%) 83/150 (55%)	29/50 (58%) S.D. = 6.43	24/50 (48%)
ALL ORGANS: HEMANGIOMA TOTAL % INCIDENCE	0/50 (0%) 1/150 (1%)	1/50 (2%) S.D. = 1.15	0/50 (0%)	1/50 (2%) 2/150 (1%)	1/50 (2%) S.D. = 1.15	0/50 (0%)
ALL ORGANS: HEMANGIOSARCOMA TOTAL % INCIDENCE	3/50 (6%) 7/150 (5%)	1/50 (2%) S.D. = 2.31	3/50 (6%)	2/50 (4%) 4/150 (3%)	2/50 (4%) S.D. = 2.31	0/50 (0%)
ALL ORGANS: HEMANGIOSARCOMA OR HEMANGIOMA TOTAL % INCIDENCE	3/50 (6%) 8/150 (5%)	2/50 (4%) S.D. = 1.15	3/50 (6%)	3/50 (6%) 5/150 (3%)	2/50 (4%) S.D. = 3.06	0/50 (0%)
ALL ORGANS: HISTIOCYTIC SARCOMA TOTAL % INCIDENCE	0/50 (0%) 0/150 (0%)	0/50 (0%) S.D. = 0.00	0/50 (0%)	0/50 (0%) 0/150 (0%)	0/50 (0%) S.D. = 0.00	0/50 (0%)
ALL ORGANS: LEUKEMIA: LYMPHOCYTIC, MONOCYTIC, MONONUCLEAR, OR UNDIFFERENTIATED TOTAL % INCIDENCE	1/50 (2%) 1/150 (1%)	0/50 (0%) S.D. = 1.15	0/50 (0%)	0/50 (0%) 0/150 (0%)	0/50 (0%) S.D. = 0.00	0/50 (0%)
ALL ORGANS: MALIGNANT LYMPHOMA AND HISTIOCYTIC SARCOMA TOTAL % INCIDENCE	5/50 (10%) 15/150 (10%)	5/50 (10%) S.D. = 0.00	5/50 (10%)	12/50 (24%) 41/150 (27%)	16/50 (32%) S.D. = 4.16	13/50 (26%)
ALL ORGANS: MALIGNANT LYMPHOMA: HISTIOCYTIC, LYMPHOCYTIC, MIXED, NOS, OR UNDIFFERENTIATED CELL TYPE TOTAL % INCIDENCE	5/50 (10%) 15/150 (10%)	5/50 (10%) S.D. = 0.00	5/50 (10%)	12/50 (24%) 41/150 (27%)	16/50 (32%) S.D. = 4.16	13/50 (26%)
ALL ORGANS: MESOTHELIOMA BENIGN, MALIGNANT, NOS TOTAL % INCIDENCE	0/50 (0%) 0/150 (0%)	0/50 (0%) S.D. = 0.00	0/50 (0%)	0/50 (0%) 0/150 (0%)	0/50 (0%) S.D. = 0.00	0/50 (0%)

*: DENOMINATOR IS NUMBER OF ANIMALS WITH TISSUES EXAMINED MICROSCOPICALLY
#: DENOMINATOR IS NUMBER OF ANIMALS NECROPSIED

Conclusion

The PRC concluded that, despite the misdosing, the new mouse study was acceptable since, the incident was reported to the Agency at the point of discovery by the Registrant, at which time the Agency agreed that the study could be continued.

Although the tumors occurring at the low dose were considered to be difficult to interpret, nevertheless, it was agreed that they could not be discounted. The PRC unanimously concluded that this new information does not affect the existing classification of Parathion as **Group C (possible human carcinogen), without quantification,** which is to say: without the use of a low dose exrapolation model (Q1*) for quantitative risk assessment; instead a reference dose (RfD) approach will be used.

Previously submitted data, and its contribution to the weight of evidence for Parathion, were fully discussed in the memos documenting Peer Review Meetings 1 and 2 (dated Sept. 8, 1986 and July 31, 1989, respectively).

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Chemical:	**Parathion**
PC Code:	**057501**
HED File Code	***21200 PEER REVIEW***
Memo Date:	**06/18/1991**
File ID:	**00000000**
Accession Number:	**412-01-0123**

HED Records Reference Center
03/20/2001